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INSIDE THIS ISSUE

SGLT-2's IN HEART FAILURE

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Sodium-glucose CoTranporter-2 Inhibitors (SGLT-2) were initially developed for the treatment of type 2 diabetes. Working to reduce renal tubular glucose reabsorption, SGLT-2 inhibitors lower blood glucose levels without stimulating the release of insulin, resulting in an average A1C reduction of 0.5%-0.8%.[1] From this class, two medications (dapagliflozin and empagliflozin) have recently shown promise in the management of heart failure. Data for the use of SGLT2 inhibitors in heart failure first began to emerge from the EMPA-REG OUTCOME trial published in 2015 where empagliflozin showed an early reduction in cardiovascular endpoints including cardiovascular death and hospitalization for heart failure-related complications[2]. Because of these outcomes, investigators postulated that the medications may potentially show benefit in patients with pre-existing heart failure which led to the induction of the DAPA-HF and EMPEROR- Reduced Trials.

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) randomized 4,744 patients with NYHA class II, III, or IV heart failure and an ejection fraction of 40% or less to receive dapagliflozin 10mg daily or placebo with about 50% of the study population having pre-existing diabetes. The primary outcome of the trial was worsening heart failure defined as need for hospitalization, urgent visit resulting in intravenous therapy for heart failure, or cardiovascular death, with a median follow-up period of 18.2 months. The primary outcome occurred in 386 of 2,373 (16.3%) in the treatment group compared to 502 of 2,371 (21.2%) of patients in the placebo arm [95% CI 0.65-0.85, p<0.001] demonstrating a reduction in heart failure progression in the treatment group regardless of the presence of diabetes.[3]

Following the completion of the DAPA-HF trial, more research was felt to be needed in specific heart failure subgroups, specifically, patients with poor renal function or severely reduced ejection fractions. This prompted the Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure Trial (EMPEROR-Reduced). EMPEROR- Reduced targeted a similar patient population as DAPA-HF with the addition of a stricter NT-proBNP (N-terminal pro-B-type naturetic peptide) eligibility criteria. The narrower inclusion criteria aimed to target patients with more advanced heart failure (mean baseline EF 27% compared to 31% in DAPA-HF). With a median follow up of 16 months, results from EMPEROR-Reduced were strikingly similar to DAPA-HF with the primary outcome occurring in 361 of 1,863 (19.4%) in the empagliflozin group and 462 of 1,867 (24.7%) of patients in the placebo arm [95% CI 0.65-0.86, p<0.001][4]. Collectively the trials showed absolute risk reductions of 3.9 and 5.2 per 100 person-years respectively (NNT 19 and 21).

Although the results of these two trials were compelling, many clinicians still questioned when to initiate the therapies and if rapid initiation following hospital discharge for a heart failure exacerbation was warranted. From this emerged the Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure (SOLOIST-WHF) trial. Twelve hundred

and twenty-two patients were randomized to sotagliflozin or placebo at hospital discharge with a primary endpoint of death from cardiovascular causes, re-hospitalization, or need for urgent medical attention related to heart failure. The primary endpoint was achieved in 245 of 608 (40.2%) patients in the treatment group and 355 of 614 (57.8%) patients in the placebo group [95% CI 0.52-0.85, p<0.001] demonstrating a significant reduction in deaths and hospitalizations when SGLT-2 therapy was initiated at hospital discharge following an acute exacerbation.[5]

While the mechanism of action for glycemic control is relativity straightforward, the pathophysiological benefits in heart failure are less clear. Several theories have been proposed including blood pressure lowering effects, anti-inflammatory properties, increased natriuresis, decreased fat mass around the heart, as well as improvement in cardiac energy metabolism; however definitive research is still underway.[6] From a safety profile, SGTL2 inhibitors do carry a risk of hypoglycemic events, however, the risk is most profound in patients on concomitant sulfonylurea or insulin therapy. Other notable risks of SGLT2 inhibitors include the risk of urinary tract infections due to increased urinary glucose levels[7]. Because of the increased natriuresis effect, some experts suggest an initial dose reduction of the patient's diuretic therapy when initiating the SGLT2 inhibitors to prevent dehydration which may have the potential to lead to kidney injury and increased incidence of urinary tract infections[8].

Although the SGLT-2 Inhibitors were originally developed to manage hyperglycemia in patients with type 2 diabetes, multiple trials have consistently found reductions in heart failure exacerbations and the need to seek urgent medical care related to heart failure, as well reductions in cardiovascular death in heart failure patients both with and without preexisting diabetes.

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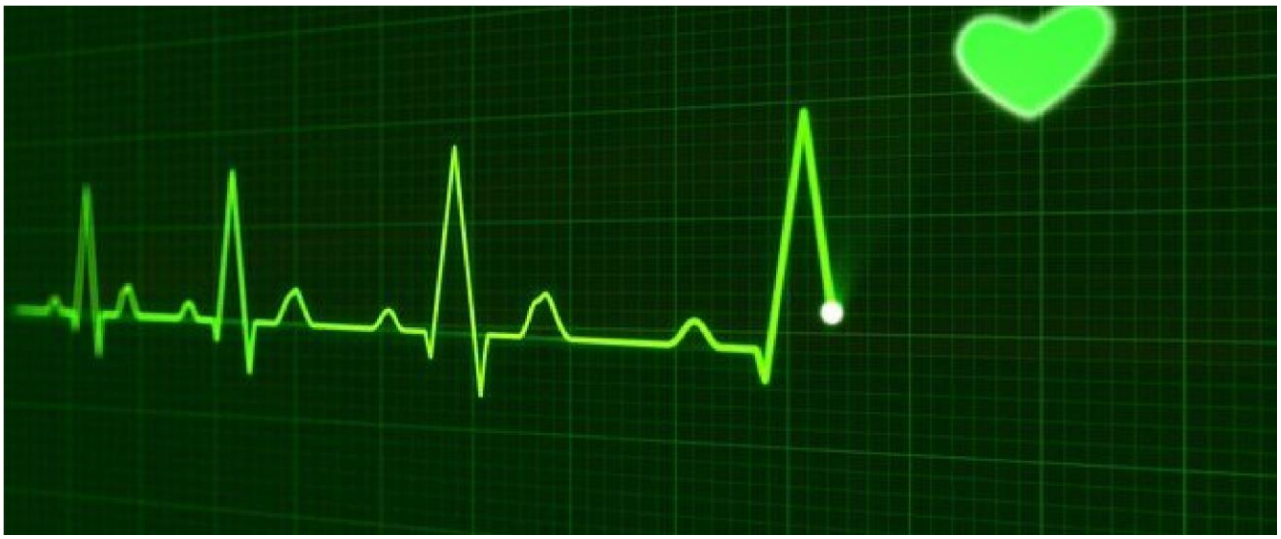

ADUCANUMAB (ADUHELM®) CONTROVERSY AND APPROPRIATE USE GUIDANCE

Tiffany Davis, PharmD, TTS

Aducanumab (Aduhelm®),[1] a monoclonal antibody directed to the N-terminus of the amyloid-beta peptide, was approved by the FDA in June 2021. Although the FDA has restricted the use of this controversial medication to patients with mild cognitive impairment or mild dementia, no other use guidance was established alongside approval.

Why the controversy? Aducanumab's (Aduhelm®) accelerated approval has sparked debate regarding both efficacy concerns (approval based on a surrogate marker and not a clinical outcome)[2,3] and a potential "inappropriately close relationship"[4] between the FDA and the pharmaceutical industry. The turmoil has led to the resignations of several FDA advisory committee members as well as refusals to provide or prescribe the medication by some medical institutions (Cleveland Clinic and Mount Sinai Health System) and physicians.[4] In fact, only around 50 centers5 in the US have administered the medication as of September, three months after its approval.

Additionally, at this time, a few Blue Cross Blue Shield plans have stated that they will not reimburse the estimated $56,000 a year drug costs.4,6 In July, the Centers for Medicare and Medicaid Services (CMS) began working through its National Coverage Determination analysis in order to determine how to cover the drug.[7]

Meanwhile, the Alzheimer's Association supports Aducanumab's (Aduhelm®) approval and use8 but is not happy with the price set by Biogen, the drug's US manufacturer. The Society for Post-Acute and Long-Term Care Medicine (ADMA) does not endorse prescribing Aducanumab (Aduhelm®) to post-acute and long-term care (PALTC) residents or patients citing the lack of evidence of benefit, potentially dangerous side effects, and high costs of not only the drug itself but also the neuroimaging required for utilization.[8-10]

To address many of these concerns the FDA published a perspective article 11 regarding the approval of Aducanumab. In the viewpoint piece, it was established that the FDA's Peripheral and Central Nervous System Advisory Committee determined that the clinical trial data did not "convincingly demonstrate a clinical benefit in reducing the clinical decline in patients with Alzheimer's disease."[11] The statement's keyword was "convincingly" since available evidence was "strongly suggestive of benefit" but complicated and in some respects contradictory, thus casting doubt on clinical benefit. The FDA's accelerated approval pathway is "intended to provide earlier access to drugs for serious disease when there is residual uncertainty at the time of approval regarding the drug's ultimate clinical benefit."[11] As expected, the accelerated approval pathway recognizes the uncertainty (surrogate endpoint effect is reasonably likely to predict clinical benefit) but also understands that certain diseases still have unmet medical needs. Patients with Alzheimer's disease need medications that address disease progression and loss of function, and they need it now. After weighing the benefits and the risks, the FDA determined that an approval delay would result in irreversible losses in memory and cognition that may have been prevented. Nonetheless, the FDA is also requiring Biogen Inc to conduct a post-approval trial to verify the benefit.

In July, the first appropriate use recommendations were published in the Journal of Prevention of Alzheimer's Disease (JPAD).[12] The Expert Panel has developed extensive recommendations based on "participant participation, conduct of the pivotal trials of aducanumab, updated prescribing information, and expert consensus."[12] The thirteen-page document focuses on how to select appropriate patients (and specifically which patients should not receive the medication), dosing and titration recommendations, side effect monitoring and management, effectiveness assessment, and therapy discontinuation. Additionally, the recommendations address concomitant use with other Alzheimer's drugs and in patients with moderate to severe disease. The impact of psychiatric, neurologic, and medical diseases on aducanumab use is also discussed. Further, the guidance document focuses on the effort needed to engage diverse populations from underrepresented communities as a measure to ensure "equity of treatment availability." [12] The journal of the Alzheimer's Association, Alzheimer's & Dementia, has since created a summary of the JPAD recommendations. Both the summary and the complete recommendation can be found at https://www.alz.org/professionals/health-systems-clinicians/appropriate-use-recommendations-for-aducanumab.

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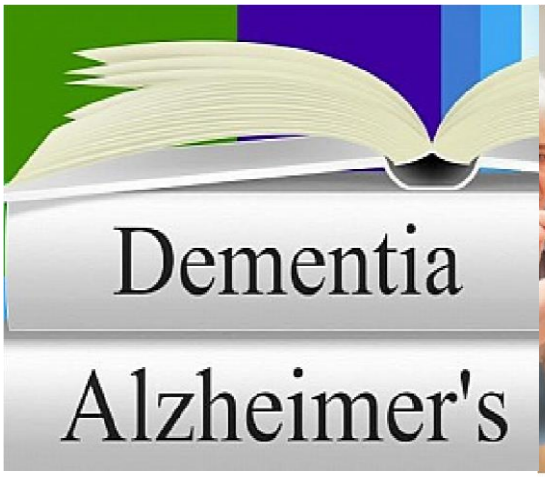
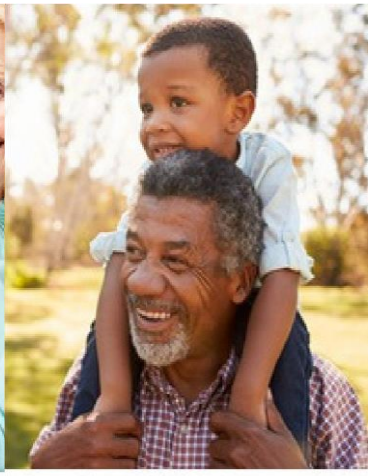




THE WHO, WHAT, WHEN, AND HOW OF LINEZOLID INDUCED THROMBOCYTOPENIA

By Kenneth Canipe PharmD, BCCCP

Introduction

Thrombocytopenia is defined as a platelet count of less than 150,000 PLT per cubic millimeter or a 50% decrease in the count from the patient's baseline.[1] Causes for thrombocytopenia include various types of cancer, viral infections, genetic conditions, and anemias. One of the often-overlooked causes is actually drug induced thrombocytopenia. The reason drug induced thrombocytopenia (DITP) goes unnoticed is because it tends to be a diagnosis of exclusion. While we have identified several medications linked to DITP such as heparin, chemotherapy agents, and interferon, these medications are ordinarily limited to the inpatient population.[1] One of the most common causes of DITP that is utilized in both an inpatient and outpatient setting is linezolid.[3] Linezolid is an oxazolidinone antibiotic typically used to treat gram positive infections, more specifically methicillin resistant Staphylococcus aureus (MRSA) or vancomycin-resistant Enterococcus (VRE).[5,6,14] Due to its favorable pharmacokinetics, 100% bioavailability, and coverage of resistant organisms it is a reasonable choice that is often selected and utilized for longer periods of time in patients suffering from infections the aforementioned organisms.[2, 14]

Risk Factors and Timing

While the above-mentioned properties make linezolid seem like an attractive choice for treating patients, we must also remember the risk of DITP and its potential consequences. Thrombocytopenia was originally reported at 3% of patients who received linezolid in clinical trials.[7] The recommendations by the manufacture in regards to this include monitoring the platelet counts in patients who have preexisting thrombocytopenia, patients at an increased bleeding risk, patients who are taking other medications that may decrease platelet counts further, and patients who have been receiving linezolid for at least two weeks or greater.[7] However, as the utilization of this medication has progressed, it was determined that the instance of linezolid induced thrombocytopenia is greater than 3% and has been reported to range anywhere from 15% to 50%.[8]

In addition to the increased instance from the original clinical trials, there has been a host of additional risk factors that have been identified as to having an association with an increased risk of linezolid induced thrombocytopenia.[9] A study by Natsumoto and colleagues identified additional risk factors including: prolonged treatment duration (greater than 10 days), renal insufficiencies, chronic liver disease, malignancy, previous vancomycin use, and lower actual body weight (ABW <60 kg).8 Previously a phase 3 trial demonstrated that the pharmacokinetics of linezolid was not influenced by renal function (creatinine clearance greater than 30 mL/min).[8] This was further reinforced when Brier and colleagues found no difference in the pharmacokinetic properties of linezolid between healthy subjects and patients who had varying levels of renal function.[15] However, an article published by Tsuji and colleagues discussed a possible link between increased area under the concentration time curve (from 0 to 24 hours) and decreased renal function.[4] Linezolid is metabolized via oxidation of the morpholine ring, yielding two inactive metabolites and approximately 30-40% of the drug is excreted unchanged in the urine.[14] The results of the Tsuji and colleagues study demonstrated that blood concentrations of linezolid were about 2-8 times higher in patients with reduced renal function as well as the instance of thrombocytopenia being higher.[4] These results were again replicated by Natsumoto and colleagues.[8] While there is currently no recommendation for dose reductions in patients with renal impairment, there is evidence to suggest that these patients may be at an increased risk of thrombocytopenia.[3,5] Natsumoto and colleagues also identified an association between lower actual body weight (53.64 kg vs 64.75 kg) and increased risk of thrombocytopenia.[8] The association's proposed mechanism is similar to that of renal impairment in that the patient is experiencing a higher plasma concentration leading to increased drug exposure.[3,5,8]

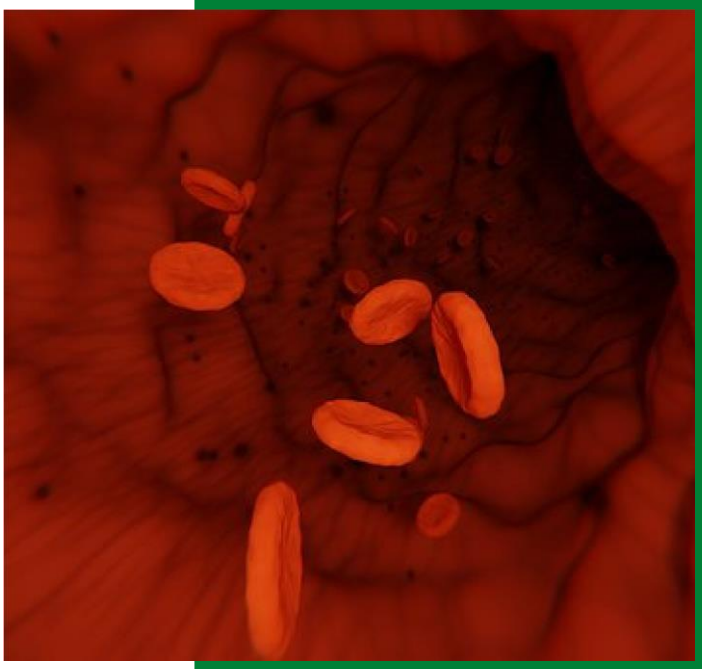
Mechanism

The mechanism responsible for linezolid induced thrombocytopenia was originally thought to be secondary to reversible myelosuppression.[7,11] Despite this being the leading proposed mechanism, there is evidence to suggest that patients who are diagnosed with thrombocytopenia due to linezolid still retain megakaryocytes in their bone marrow, therefore muddying the water of the original proposed mechanism.[3,9,11] A case report by Bernstein and colleagues discusses a patient suspected of experiencing linezolid induced thrombocytopenia and the in-depth investigation to finding a mechanism.[3] The authors noted that a bone marrow biopsy and aspiration showing no evidence of "direct marrow toxicity" (no abnormal morphology or reduced megakaryocytes). Instead, they suggested that anemia and thrombocytopenia were due to a similar mechanism as

Table 1 Naranjo Adverse Drug Reaction Scale[12,13]

	Yes	No	Do Not Know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
Did the reaction appear when a placebo was given?	-1	+1	0	
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic	+1	0	0	
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased	+1	0	0	
Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0	
Was the adverse event confirmed by the objective evidence?	+1	0	0	
Definite: ≥ 9, Probable: 5-8, Possible: 1-4, Doubtful: 0				

chloramphenicol-induced myelosuppression. The proposed mechanism was suggested to be due to "suppression of mitochondrial respiratory via inhibition of mitochondrial protein synthesis".[3]



Diagnosis

The diagnosis of linezolid-induced thrombocytopenia requires a multistep approach. The first step in this process is exclusionary, rule out other potential causes. This step is especially critical if thrombocytopenia occurs early with therapy as linezolid induced thrombocytopenia tends to occur after approximately 10-14 days. [5,7,9] Once all other causes have been ruled out and there is a high degree of suspicion that linezolid has induced the thrombocytopenia, there are various methods to estimate the probability of a drug induced adverse reaction.[12,13]

The gold standard for estimating an adverse event due to medication is the Naranjo Adverse Drug Reaction (see table 1), with the higher the score leading to a higher probability of the drug causing the reaction.[12]

Recovery

Once the adverse drug event has been discovered, the primary step in treatment will be either stopping the therapy all together or switching to an alternative antibiotic regimen, should the patient still require treatment. Case studies published by Wang and colleagues as well as Ebeling and colleagues discussed the clinical course of their patients once the medication was removed.[10,11] Ebeling and colleagues demonstrated a return to baseline of their patient's platelets approximately one week after medication discontinuation.[11] Their patient did not require any platelet transfusions or other supportive care during the recovery phase.[11] Wang and colleagues discussed a patient that demonstrated linezolid induced thrombocytopenia after 16 days of therapy that yielded a nadir platelet count of 15 x109/L.[10] Despite the transfusion and supportive care, the patient still required approximately 13 days for their platelet count to return to normal.10 The patient was then re-challenged with linezolid yielding the same result (a nadir of 5x109/L) on day 9 of therapy.[10] Once the medication was discontinued again the patient's platelet counts recovered within 14 days. A retrospective cohort study performed by Kawasuji and colleagues discussed the recovery of 9 patients that also experienced linezolid induced thrombocytopenia.[3] Of the 9 cases they discussed 8 of the patients had a normal platelet count at the end of linezolid treatment.[3] The sole remaining patient's platelet count required 11 days after treatment discontinuation to recover.[3]

Conclusion

While linezolid is an attractive option to manage patients with MRSA and VRE it is not without its risks. It is important to keep in mind which patients may be at a

higher risk for the development of linezolid induced thrombocytopenia and ensure that the benefits outweigh the risks. Maintaining shorter treatment durations (less than 14 days)[7] when appropriate will help to minimize the potential for thrombocytopenia in addition to adhering to antibiotic stewardship and preventing resistance. Should a patient develop linezolid induced thrombocytopenia, the discontinuation of therapy should result in resolution of the thrombocytopenia within approximately 1-2 weeks based on the available literature.[3,10,11]

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